

Applicant(s): Sandor LOVAS et al.

Serial No.: Unassigned (Parent: 09/269,954)

Filed: Herewith (Parent: 08 April 1999)

For: NOVEL GnRH ANALOGUES WITH ANTITUMOR EFFECTS AND PHARMACEUTICAL COMPOSITIONS THEREOF

### Amendments to the Claims

This listing of claims replaces all prior versions, and listings, of claims in the above-identified application:

#### Listing of Claims

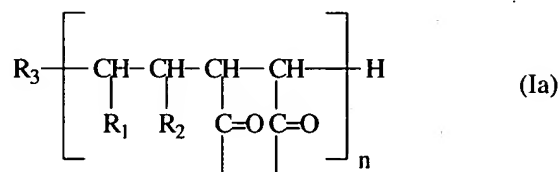
1-17. (Canceled)

18. (Original) A pharmacologically active compound of formula (I)

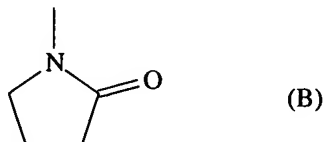


wherein

Y represents the molecular moiety of formula (Ia),



wherein n is an integer from 10 to 400; one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen atom whereas the other one represents a group of formula (B);



R<sub>3</sub> represents a polymerization-initiating group;

W represents a hydroxyl group, optionally as a salt formed with an alkali metal ion;

V represents a C1-8 alkylamino group bonded through its amino group or a valence bond;

X is a "spacer" group being an amino acid group or an oligopeptide group of at most six members wherein the amino acid or oligopeptide group is coupled through its N-terminal to the Y group and

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is optionally bearing a hydroxyl group or a valence bond on its C-terminal, wherein the amino acids are Gly, Ala, Leu, Ile, Val, Phe, Tyr, Ahx, Pro, Arg, or His;

A is present and represents a pharmacologically active polypeptide hormone group containing an amino group and directly coupled therethrough to the Y group when r is 0; or coupled to the C-terminal of the X group, respectively, when r is larger than 0;

r is an integer from 0 to 0.2 n;

k is an integer being at most equal to r; z is an integer from 0 to (n-r); and

u is an integer from n to 2n-r-z, as well as the salts and complexes of these compounds.

19. **(Original)** The pharmacologically active compound of formula (I) of claim 18, wherein R<sub>3</sub> is a (CH<sub>3</sub>)<sub>2</sub>CCN group.

20. **(Original)** The pharmacologically active compound of formula (I) of claim 19, wherein:

A represents a native gonadotropin-releasing hormone (GnRH) coupled through its amino group or a pharmacologically active analogue thereof; and k, r, u, z, X, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.

21. **(Original)** The pharmacologically active compound of formula (I) of claim 20, wherein

A represents

pGlu-His-Trp-Ser-His-Asp-Trp-Lys-Pro-Gly-NH<sub>2</sub> (SEQ ID NO:2),

Ac-D-Trp<sup>1,3</sup>, p-chlorophenyl-D-alanine<sup>2</sup>(D-Cpa<sup>2</sup>), D-Lys<sup>6</sup>, D-Ala<sup>10</sup>-gonadotropin-releasing hormone (GnRH)

Ac-D-Trp<sup>1,3</sup>, D-Cpa<sup>2</sup>, Lys<sup>5</sup>, [Asp(a-DEA)]<sup>6</sup>, D-Ala<sup>10</sup>-Gln<sup>8</sup>-GnRH,

D-Phe<sup>2</sup>, D-Trp<sup>3</sup>, D-Lys<sup>6</sup>-GnRH,

Lys<sup>5</sup>, cyclo(Asp<sup>6</sup>-Lys<sup>8</sup>)-GnRH-III,

Lys<sup>4</sup>, [Lys(ε-Fmoc)]<sup>8</sup>-GnRH-III,

Lys<sup>4</sup>-GnRH-III,

D-Lys<sup>6</sup>-GnRH,

Lys<sup>5</sup>, D-Trp<sup>6</sup>-GnRH

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coupled to X or Y through the  $\epsilon$ -amino group of their Lys side chains; and k, r, u, z, X, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.

22. **(Original)** The pharmacologically active compound of formula (I) of claim 18, wherein X represents an oligopeptide group consisting of four members; and k, r, u, z, A, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.
23. **(Original)** The pharmacologically active compound of formula (I) of claim 18, wherein X represents an oligopeptide group consisting of three members; and k, r, u, z, A, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.
24. **(Original)** The pharmacologically active compound of formula (I) of claim 18, wherein V is a C4-6 alkylamino group.
25. **(Original)** The pharmacologically active compound of formula (I) of claim 18, wherein r is 0; and k, u, z, A, Y, V and W are as defined in claim 18, as well as the salts and complexes of these compounds.
26. **(Original)** A compound containing an activated ester group of formula (Ic),
- $$Y[W_u, V'_z, (XOQ)_r] \quad (Ic)$$
- wherein Y represents the molecular moiety of formula (Ia), wherein n is an integer from 10 to 400; one of R<sub>1</sub> and R<sub>2</sub> represents hydrogen atom whereas the other one represents a group of formula (B); R<sub>3</sub> represents a polymerization-initiating group; W represents a hydroxyl group, optionally as a salt formed with an alkali metal ion; V' represents a C1-8, alkylamino group bonded through its amino group; X represents an amino acid group or an oligopeptide group of at most six members coupled through its N-terminal to the Y group; OQ represents an activated ester group on C-terminal of the X group; r is an integer from 0 to 0.2 n; z is an integer from 0 to (n-r); and u is an integer from n to (2n-r-z), as well as the salts of these compounds.

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27. **(Original)** Compounds of formula (Ic) as claimed in claim 26, wherein X represents an oligopeptide group consisting of at most four members, preferably -Gly-Phe-Leu-Gly-, -Gly-Phe-Gly-, -Phe-Leu-Gly- or -Ahx-; OQ represents ONp group; and k, r, u, z, A, Y, V' as well as W are as defined in claim 26, as well as the salts of these compounds.
28. **(Original)** A pharmaceutical composition comprising a compound of formula (I) of claim 18, wherein k, r, u, z, X, Y, V and W are as defined in claim 18, or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.
29. **(Original)** A tumour-inhibiting pharmaceutical composition comprising a compound of formula (I) of claim 20 or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.
30. **(Original)** A tumour-inhibiting and immunostimulatory pharmaceutical composition comprising a compound of formula (I), wherein A represents Ac-D-Trp<sup>1,3</sup>, p-chlorophenyl-D-alanine<sup>2</sup>(D-Cpa<sup>2</sup>), Lys<sup>5</sup>, [Asp(a-DEA)]<sup>6</sup>, D-Ala<sup>10</sup>-Gln<sup>8</sup>-GnRH, and k, r, z, u, X, Y, V and W are as defined in claim 18, or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.
31. **(Original)** A composition comprising a compound of claim 18 in combination with a pharmaceutically acceptable carrier.
32. **(Original)** The pharmacologically active compound of claim 18, wherein n is an integer from 20 to 200.
33. **(Original)** The pharmacologically active compound of claim 22, wherein X represents -Gly-Phe-Leu-Gly- (SEQ ID NO:5).

**Preliminary Amendment**

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34. **(Original)** The pharmacologically active compound of claim 23, wherein X represents -Phe-Leu-Gly-.
35. **(Original)** The pharmacologically active compound of claim 23, wherein X represents -Gly-Leu-Gly-.
36. **(Original)** The compound of claim 26, wherein n is an integer from 20 to 200.
37. **(Original)** The compound of claim 26, wherein  $R_3$  represents  $(CH_3)_2CCN$ .
38. **(Original)** The compound of claim 26, wherein W represents a hydroxyl group as a salt formed with a sodium ion.
39. **(Original)** The compound of claim 26, wherein V' represents a C4-6 alkylamino group.
40. **(Original)** The compound of claim 26, wherein the activated ester group is selected from the group consisting of ONp, OPcp, Opfp, and ONsu.
41. **(Original)** A tumour-inhibiting pharmaceutical composition comprising a compound of formula (I) of claim 21 or a pharmaceutically acceptable salt or complex thereof in admixture with carriers and/or additives commonly used in the pharmaceutical industry.